METHOD OF TREATING IMMUNOINFLAMMATORY DISEASE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation in part of Ser. No. 07/761,120, filed Sept. 17, 1991 and now abandoned

BACKGROUND OF THE INVENTION

Skin diseases such as contact hypersensitivity, atopic dermatitis, and psoriasis are characterized by hyperproliferative and inflammatory skin disorders. A large population suffers from these disorders, psoriasis; for example, afflicts approximately 2% of the population in Western countries [Ziboh, V. A. Psoriasis: Hyperproliferative/Inflammatory skin disorder, Drug Development Research 13: 137–146, (1988)]. Human skin diseases like psoriasis are characterized by histopathologically distinct patterns of infiltration by T cells, B cells, monocytes and granulocytes. These leukocyte cell infiltrations are the consequence of expression of intercellular adhesion molecules and release of cytokine and chemotactic factors by nonhematopoietically derived cells (e.g. keratinocytes) of the skin which in turn augment hyperplasia.

Current treatment of immunologically mediated skin disorders involves the use of antiinflammatory agents such as glucocorticoids and antiproliferative agents such as methotrexate, 5-fluorouracil, and retinoids. Recently, use of the immunosuppressive agent cyclosporin A has been reported to give clinical improvement of psoraisis. [Ellis, J. Am. Med. Assoc. 256: 3110–3116, (1986)]. However, its usefulness in psoriasis is limited due to high incidence of nephrotoxicity [Ellis, New England J. Med. 324: 277–84, (1991)], and the observation of relapse after cessation of the treatment with cyclosporin A [Griffiths, J. Am. Acad. Dermatol. 23: 1242–1247, (1990)].

Rapamycin, a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus* [U.S. Pat. No. 3,929,992] has been shown to prevent the formation of humoral (IgE-like) antibodies in response to an albumin allergic challenge [Martel, R., Can. J. Physiol. Pharm. 55: 48 (1977)], inhibit murine T-cell activation [Staruch, M., FASEB 3: 3411 (1989)], and prolong survival time of organ grafts in histoincompatible rodents [Morris, R., Med. Sci. Res. 17: 877 (1989)].

DESCRIPTION OF THE INVENTION

This invention provides a method of treating immunoinflammatory skin disease in a mammal in need thereof which comprises administering an antiimmunoinflammatory amount of rapamycin orally, parenterally, intranasally, intrabronchially, topically, transdermally, or rectally. In particular, rapamycin is useful in providing symptomatic relief of, preventing the progression of, or eradicating inflammatory skin disease. As such, rapamycin is useful in treating skin diseases such as psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrheic dermatitis, Lichen planus, Pemphigus, bulus pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinphilias, and the like.

The effect of rapamycin on skin disease was established in two in vivo standard animal pharmacological test procedures emulating skin immunoinflammatory diseases observed in mammals. The procedures used and results obtained are described below.

The first in vivo standard pharmacological test procedure measured the effect of rapamycin on dermal inflammation, as measured by the prevention of tetradecanoylphorbol acetate (TPA) induced ear edema in Webster mice. Cyclophosphamide, cyclosporin (CsA), indomethacin, and BW755C also were evaluated for the purpose of comparison. The following briefly describes the procedure used.

Female Swiss Webster mice (Buckshire; 8 weeks old) were divided into groups of six. Tetradecanoylphorbol acetate (TPA) were dissolved in acetone at concentrations of 200 μg/ml. Each mouse received 4 μg/ear of TPA on the right ear. These suboptimal doses of phlogistics were applied by an automatic pipette in 10 μl volumes to both the inner and outer surfaces of the ear. The left (control) received acetone or vehicle. Drugs were applied topically in acetone and in some cases 95% ethanol was used to solubilize the drug prior to dilution with acetone. Topical drug regimen was as follows: drugs were given 30 min. after treatment with TPA. Edema measurements were taken with an Oditest calipers. The thickness of the right and left ears were usually measured in units of 0.01 mm 4 h after TPA application. Ear edema was calculated by subtracting the thickness of the left ear (vehicle control) from right ear (treated ear).

The results obtained in the TPA induced ear edema standard pharmacological test procedure are shown in the following table.

Treatment Group	Dose (mg/ear)	Mean Edema (mm^{-2} ± SEM)	Percent Change
Control		28.3 ± 1.1	—
Rapamycin	0.25	17.8 ± 4.1	−37.1*
Rapamycin	1.0	12.0 ± 2.5	−57.6*
Cyclophosphamide	0.25	16.5 ± 3.1	−41.7*
Cyclophosphamide	1.0	15.0 ± 2.4	−47.0
Cyclosporin A	0.25	23.8 ± 2.0	−15.9
Cyclosporin A	1.0	26.0 ± 1.3	−7.1
Indomethacin	0.5	12.0 ± 2.3	−57.6*
BW755C	0.5	12.0 ± 2.4	−57.6*
BW755C	1.0	12.7 ± 1.4	−55.1*

*Statistically significant ($p \leq 0.05$) difference from control mice.

The results of this standard pharmacological test procedure showed that rapamycin significantly ($p \leq 0.05$) prevented an acute inflammatory response following topical TPA administration. Cyclosporin A, an immunosuppressive agent typically compared with rapamycin, prevented the inflammatory response to a much lesser extent.

The second in vivo standard pharmacological test procedure measured the effect of rapamycin on preventing oxazolone-induced contact hypersensitivity of the mouse ear. This test procedure emulates the inflammatory response observed in immunoinflammatory diseases of the skin in mammals. The following briefly describes the procedure used and results obtained. Dexamethasone, and cyclosporin A also were evaluated for the purpose of comparison.

Female, Swiss Webster mice (8 weeks old) were placed into groups of 6 and the abdominal area of each was shaved. The mice were sensitized to oxazolone (4-ethoxymethylene-2-phenyl-oxazol-5-one) by applying 100 μl of a 2% solution in 95% alcohol directly onto the shaved abdomen using an automatic pipette and rubbing the residual oxazolone into the skin with a